## THE REMARKS

**The Amendment**

Prior to entering the amendments, Claims 1-34 are pending.

Applicants apologize to the Examiner that numerous minor amendments are made in the specification and in the claims. Most of the amendments merely correct obvious typographical errors. The amendments are necessary to present the application in a correct manner.

Applicants have amended the specification and in Claim 1 to recite that B' is a purine or a pyrimidine residue according to general formulas IV and V that is linked to the 1' position (not 5' position) or the furanose or carbocycle via the 9- or 1- position, respectively. Support for the amendment can be found in the chemical structure of Formula I and Ia, which show B is linked to the 1' position of the furanose or carbocycle.

In the specification and in Claim 1, the sum of m+n+p is amended from "1 to 5" to "0 to 5." Support for the amendment can be found, for example, page 6, lines 14-16, where it states m= 0, 1, or 2; n= 0 or 1; p= 0, 1, or 2. Therefore, the lower limit of the sum of m+n+p is 0. The amendment is further supported by Example 4 (page 25), which shows the synthesis of a monophosphate (m+n+p= 0).

In the specification and in Claim 1, "where $R_1/R_2/R_3/R_4$ falls under the definition of general formula II/III" is amended to "where $OR_1/OR_2/OR_3/OR_4$ falls under the definition of general formula II/III." Support for the amendments can be found in the general formula II/III.

The chemical structure of Formula IV in the specification at page 16 and in Claim 1 is amended to correct an obvious drawing error. The "H" atom is changed to a bond in Formula IV. The amendments are consistent with the description that Formula IV is linked to the 1' position of the furanose or carbocycle via the 9-position of the purine. Formula IV is a purine moiety, not a purine.

The chemical structure of Formula V in the specification at page 16 and in Claim 1 is amended to correct an obvious drawing error. A chemical bond is drawn from the N1 position. The amendments are consistent with the description that Formula V is linked to the 1' position of the furanose or carbocycle via the 1-position of the pyrimidine. Formula V is a pyrimidine moiety, not a pyrimidine.

At page 29, line 11, $P2Y_T$ agonist is amended to $P2Y_T$ antagonist. Support for the amendment can be found, for example, at page 5, line 20 and at page 54, line 7.

Claim 1 is amended to delete A= "cycloalkyl, aralkyl, aryl, and acylthioalkyl, with or without substituents or heteroatoms." Claim 1 is further amended to consolidate and clarify the meaning of the

claim; a better description and proviso are provided for Y', Z', Z and Y in Claim 1, which are supported by the original Claim 1 and throughout the application.

Claim 1 is amended to recite a pharmaceutical formulation. Support for the amendment can be found at page 5, lines 19-20.New Claims 35-36 recite the characteristics of the pharmaceutical formulation. Support for the amendments can be found, for example, at page 21, lines 22-23 and page 29, lines 16-19.

Claim 3 is amended to incorporate the pharmaceutical formulation of Claim 1.

New Claim 38 is a compound claim. Claim 38 is similar to the original Claim 1 except Claim 38 deletes hydroxy, oxo, amino, mercapto, alkylamino, and dialkylamino from $R_{10}$ and $R_{14}$. Claim 38 excludes some known compounds.

No new matter is added to any of the above amendments. The Examiner is requested to enter the amendments and reconsider the application.

**The Response**

**In the Specification**

The Abstract of the Disclosure is objected to because of the use of the word "novel" to describe the compounds of the invention. Applicants have amended the Abstract to delete the word "novel."

**35 U.S.C. §102 (b) Rejections**

**1. Kim, *et al.***

Claims 1 and 2 are rejected under 35 U.S.C. §102(b) as being anticipated by Kim, *et al.*, J. Biol. Chem. Vol. 269(9), pp. 6471-7. The rejection is traversed in view of the amendments because Kim, *et al.* do not teach the claimed formulation or compounds.

Kim, *et al.* disclose purinergic receptors of adenosine 5'-O-(1-thiotriphosphate), adenosine 5'-O-(3-thiotriphosphate), 3'-O-(4-benzoyl-benzoyl)ATP, α,β- and β,γ-methylene ATP.

In the instant Claim 1, when A= M (H or a pharmaceutically-acceptable inorganic or organic counterion) or alkyl; the claimed compound is a mononucleoside polyphosphate (Formula Ib). The claimed compounds are unique in that Y'= H, OH, or $OR_1$, where $OR_1$ falls under the definition of general formula II or III;

Z'= H, OH or $OR_2$, where $OR_2$ falls under the definition of general formula II or III;

**with the provision that at least one of Y' and Z' is $OR_1$ or $OR_2$.**

With the proviso, one of Y' or Z' is an ether, ester, thioester, carbamate, thiocarbamate, cyclical acetal, cyclical ketal, or cyclical orthoester. Kim, *et al.* only disclose 3'-O-(4-benzoyl-benzoyl)ATP, in which Y' is an aryl-aryl ester. Applicants has amended Claim 1 to delete $R_7$ being aryl or substituted aryl when $R_5$ and $R_6$ are taken together to be oxygen or sulfur doubly bonded to Q. Therefore, Kim, *et al.* do not teach Formula I compound in Claim 1. Further, Kim, *et al.* do not teach a pharmaceutical formulation comprising Formula I compound.

Therefore, the §102(b) rejection of Claims 1 and 2 over Kim, *et al.* should be withdrawn.

~~2. Yerxa, *et al.*~~

Claims 1 and 2 are rejected under 35 U.S.C. §102(b) as being anticipated by Yerxa, *et al.*, U.S. 6,323,187. The rejection is traversed because Yerxa, *et al.* do not teach the claimed compounds.

Yerxa, *et al.* disclose $P^1$-(cytidine 5')-$P^4$-(uridine 5'-)tetraphosphates.

In the instant Claim 1, when A=nucleoside, the claimed compound is a dinucleoside polyphosphate (Formula Ia). The claimed compounds are unique in that

Y'= H, OH, or $OR_1$, where $OR_1$ falls under the definition of general formula II or III;

Z'= OH or $OR_2$, where $OR_2$ falls under the definition of general formula II or III;

Z= OH or $OR_3$, where $OR_3$ falls under the definition of general formula II or III;

Y= H, OH, or $OR_4$, where $OR_4$ falls under the definition of general formula II or III;

**with the provision that at least one of Y', Z', Z and Y is $OR_1$, $OR_2$, $OR_3$, or $OR_4$, respectively.**

With the proviso, one of Y', Z', Z and Y is an ether, ester, thioester, carbamate, thiocarbamate, cyclical acetal, cyclical ketal, or cyclical orthoester. Yerxa, *et al.* only disclose $P^1$-(cytidine 5')-$P^4$-(uridine 5'-)tetraphosphates where Y, Y', Z and Z' all equal to OH. Yerxa, *et al.* do not teach the claimed compounds.

Therefore, the §102(b) rejection over Yerxa, *et al.* should be withdrawn.

**35 U.S.C. §103 Rejections**

Claims 1-34 are rejected under 35 U.S.C. §103 as being unpatentable over Yerxa, *et al.*, U.S. 6,323,187 in combination with Kim, *et al.*

Claim 4 is canceled. Claims 3 and 5-34 are directed to a method of preventing or treating diseases or conditions associated with platelet aggregation by administering to a subject a pharmaceutical formulation according to Claim 1.

**(a) The instant compounds are not taught or suggested by Yerxa, *et al.*, or Kim, *et al.*.**

As discussed above, neither Yerxa, *et al.*, nor Kim, *et al.* has taught or suggested the pharmaceutical formulation of Claim 1. Therefore, the combination of the references does not produce the claimed pharmaceutical formulation (Claim 1 and new claims 35 and 36) or the method of using the pharmaceutical formulation (Claims 3 and 5-34).

**(b) Yerxa, *et al* do not disclose $P2_T$ receptor.**

The present invention is directed to a method of preventing or treating diseases or conditions associated with platelet aggregation comprising administering to a subject a pharmaceutical formulation comprising a compound according to Formula I ($P2_T$ receptor antagonist compound), wherein said compound is effective to bind the $P2_T$ receptors on platelets and inhibit ADP-induced platelet aggregation.

Binding of ADP to platelet receptors is required for elicitation of the ADP-induced platelet aggregation. There are at least three P2 receptors expressed in human platelets: a cation channel receptor $P2X_1$, a G protein-coupled receptor $P2Y_1$, and a G protein-coupled receptor $P2Y_T$ (also referred to as $P2_T$, $P2Y_{ac}$ and $P2Y_{12}$). The $P2X_1$ receptor is responsible for rapid calcium influx and is activated by ATP and by ADP. However, its direct role in the process of platelet aggregation is unclear. The $P2Y_1$ receptor is responsible for calcium mobilization, shape change and the initiation of aggregation. $P2Y_T$ receptor is responsible for inhibition of adenylyl cyclase and is required for full aggregation. (See specification at page 2, line 31 through page 3, line 7)

Yerxa, *et al.* disclose compounds that are agonists of the $P2Y_2$ and/or $P2Y_4$ purinergic receptor. Yerxa, *et al.* do not teach or suggest $P2Y_T$ receptor antagonist.

**(c) Kim, *et al.* do not teach using $P2_T$ receptor antagonist (formula I compound) to treat platelet aggregration.**

The purpose of Kim, *et al.* is to describe "a purinergic P2 receptor on PC12 cells that does not fit the classification for the $P_2x$, $P_2y$, $P_2t$, $P_2u$, $P_2z$ receptor subtypes." (See Abstract last sentence)

Platelet aggregation is mentioned in the reference at page 6471, first paragraph under the Abstract:

> Extracellular nucleotides can influence many biological functions, including platelet aggregation, vascular tone, cell division, cardiac and skeletal muscle contraction, as well as peripheral and central neurotransmission (1). These extracellular actions of ATP are mediated through purinergic receptors that have been classified by Burnstock (2) as P2 receptors."

~~The above paragraph only discloses that ATP (an extracellular nucleotide) can influence platelet~~ aggregation. Throughout the reference, there is no teaching or suggestion that either a $P2_T$ receptor antagonist or the claimed formula I compound can be used to treat platelet aggregation.

Even with hindsight construction, the combination of Yerxa, *et al.* with Kim, *et al.* do not produced Claims 1-3 and 5-34. Therefore, the 103(a) rejections of Claims 1-3 and 5-34 should be withdrawn.

## CONCLUSION

Applicant believes that the application is in good and proper condition for allowance. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is encouraged to call the undersigned at (650) 463-8109.

Respectfully submitted,

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